IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicants: | Benny Bang-Andersen, et al. |
| Application No.: | 10/568,292 |
| Filed: | August 14, 2006 |
| Group Art Unit: | 1624 |
| Examiner: | Emily B. Bernhardt |
| Confirmation No. | 3519 |
| For: | TRANS-1-(6-CHLORO-3-PHENYLINDAN-1-YL)-3,3-DIMETHYLPIPERAZINE |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION OF **BENNY BANG-ANDERSEN, Ph.D.**, UNDER 37 C.F.R. 1.132

I, Benny Bang-Andersen, hereby declare as follows:

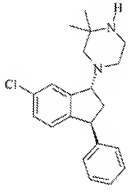
1. I am a citizen of Denmark, more than twenty-one years of age.

2. I received a Doctor of Philosophy degree in medicinal chemistry from the Royal Danish School of Pharmacy in 1997.

3. I have been employed at H. Lundbeck A/S, the assignee of the present application, for 17 years, holding a number of positions within Medicinal Chemistry Research, such as Head of Section, Head of Department, Associate Director and my current title as Group Leader/Senior Principal Scientist, which I have held since January 2009. My curriculum vitae is attached as **Exhibit A**, *infra*.

4. Klaus Peter Bogesø, Henrik Svane, Lars Ole Lyngsø, Allan Carsten Dahl, Mark Howells, Klaus Gjervig Jensen, Tomas Mow and I conceived of, and reduced to practice, the invention claimed in the above-identified patent application, as to which we have been named co-inventors.

5. I have reviewed the above-identified patent application, which provides that the invention includes a compound, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I):




(I);

or a pharmaceutically acceptable salt thereof (hereinafter referred to as "Compound I").

6. I have reviewed the Final Office Action mailed February 3 2009, in connection with the above-identified patent application, along with the November 13, 2008 response to the May 13, 2008 Office Action, including my contemporaneously submitted declaration ("my November 2008 declaration"), pending claims for the application and amended claims being submitted with a Request for Continued Examination ("RCE") with which my declaration will be contemporaneously submitted.

7. Concerns have been raised on variability of the test results submitted in Appendix A of my November 2008 declaration when comparing them over time (years). However, to ensure that the results are comparable over years, a positive control for CYP2D6 inhibition, Fluovoxamine, was included in each single run of the inhibition experiments. *See infra,* **Appendix B** for respective control results to the aforementioned test results. As declared by my co-inventor, Klaus Gjervig Jensen, in his contemporaneously submitted declaration ("the KGJ declaration").

inclusion of a positive control, as well as the fact the enzymes and test chemicals met suppliers' specifications, allows for comparison of the test results.

8. I concur with and similarly declare the statements at paragraphs 8-9 of the KGJ declaration.

9. Because of the foregoing and my statements in my November 2008 declaration, Compound I and its aforementioned property is surprising, unexpected and unpredictable over the prior art Compounds A-H.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2 March 2010
Date

Benny Bang-Andersen, Ph.D.

**Exhibit A**

CURRICULUM VITAE, BENNY BANG-ANDERSEN, Ph.D.

PERSONAL

| | |
|---|---|
| Date of birth: | 3 May 1965 |
| Address: | 33 Lillegrund, DK – 2300 Copenhagen S |
| Working address: | H. Lundbeck A/S, Medicinal Chemistry I, 9 Ottiliavej, DK – 2500 Valby |
| Phone: | +45 3643 3247 |
| Mobile phone: | +45 3083 3247 |
| E-mail: | ban@lundbeck.com |

EDUCATION

| | | |
|---|---|---|
| 2001 | The HD Graduate Diploma in Business Administration (Line of Specialization: Organisation & Management) | Copenhagen Business School, Denmark |
| 1997 | PhD in medicinal chemistry<br>Advisors: Professor Povl Krogsgaard-Larsen and DSc. Klaus P. Bøgesø | Royal Danish School of Pharmacy, Copenhagen, Denmark |
| 1993 | MSc in Pharmacy (cand. pharm.) | Royal Danish School of Pharmacy, Copenhagen, Denmark |
| 1992 | MSc with distinction in Chemical Research<br>Advisor: Professor C. Robin Ganellin | University College London, University of London, UK |

PROFESSIONAL EXPERIENCE

*Line Management*

| | |
|---|---|
| 1 Jan 09 | Group Leader/Senior Principal Scientist, Medicinal Chemistry Research (MCR) DK, H. Lundbeck A/S (*current position*) |
| 1 Feb 06 – 31 Dec 08 | Associate Director, MCR DK, H. Lundbeck A/S |
| 1 Apr 03 – 31 Jan 06 | Head of Department, Medicinal Chemistry I, MCR DK, H. Lundbeck A/S |

PROFESSIONAL EXPERIENCE

*Line Management*

1 Jan 02 - 31 Mar 03 Head of Section, MCR DK, H. Lundbeck A/S

1 Oct 96 - 31 Dec 01 Medicinal Chemist, MCR DK, H. Lundbeck A/S

*Project Management and Other Professional Experience*

15 May 99 – Dec 05 Drug Discovery Project Leader, H. Lundbeck A/S

1997- Medicinal Chemistry Team Leader, H. Lundbeck A/S

MEMBERSHIP OF PROFESSIONAL SOCIETIES AND OTHER ACTIVITIES

External Examiner (MSc and PhD projects), FARMA, University of Copenhagen.
Member of the American Chemical Society.
Member of the Danish Society for Pharmacology and Toxicology.
Member of the Danish Chemical Society.
Member of the Society for Medicines Research.

PUBLICATIONS

1. Ganellin, C. R.; Bang-Andersen, B.; Khalaf, Y. S.; Tertiuk, W.; Arrang, J. M.; Garbarg, M.; Ligneau, X.; Rouleau, A.; Schwartz, J. C.
Imetit and *N*-methyl derivatives. The transition from potent agonist to antagonist at histamine $H_3$ receptors.
*Bioorg. & Med. Chem. Lett.* **1992**, *2*, 1231-1234.

2. Madsen, U.; Bang-Andersen, B.; Brehm, L.; Christensen, I. T.; Ebert, B.; Kristoffersen, I. T. S.; Lang, Y.; Krogsgaard-Larsen, P.
Synthesis and pharmacology of highly selective carboxy and phosphono isoxazole amino acid AMPA receptor antagonists.
*J. Med. Chem.* **1996**, *39*, 1682-1691.

3. Ganellin, C. R.; Fkyerat, A.; Bang-Andersen, B.; Athmani, S.; Tertiuk, W.; Garbarg, M.; Ligneau, X.; Schwartz, J. C.
A novel series of (phenoxyalkyl)imidazoles as potent $H_3$-receptor histamine antagonists.
*J. Med. Chem.* **1996**, *39*, 3806-3813.

4. Bang-Andersen, B.; Lenz, S. M.; Skjærbæk, N.; Søby, K. K.; Hansen, H. O.; Ebert, B.; Bøgesø, K. P.; Krogsgaard-Larsen, P.
Heteroaryl analogues of AMPA. Synthesis and quantitative structure–activity relationships.
*J. Med. Chem.* **1997**, *40*, 2831-2842.

5. Vogensen, S. B.; Jensen, H. S.; Stensbøl, T. B.; Frydenvang, K.; Bang-Andersen, B.; Johansen, T. N.; Egebjerg, J.; Krogsgaard-Larsen, P.
Resolution, configurational assignment and enantiopharmacology of 2-amino-3-[3-hydroxy-5-(2-methyl-2*H*-tetrazole-5-yl)isoxazol-4-yl]propionic acid, a potent GluR3 and GluR4 preferring AMPA receptor agonist.
*Chirality* **2000**, *12*, 705-713.

6. Bang-Andersen, B.; Ahmadian, H.; Lenz, S. M.; Stensbøl, T. B.; Madsen, U.; Bøgesø, K. P.; Krogsgaard-Larsen, P.
Structural determinants of AMPA agonist activity in analogues of 2-amino-3-(3-carboxy-5-methyl-4-isoxazolyl)propionic acid (ACPA). Synthesis and pharmacology.
*J. Med. Chem.* **2000**, *43*, 4910-4918.

7. Frydenvang, K.; Sommer, M. B; Heckmann, D.; Nielsen, O.; Bang-Andersen, B.
2-(2,3-Dihydro-1*H*-indol-3-yl)ethanol: Synthesis, separation of enantiomers, and assignment of absolute stereochemistry by X-ray structure analysis.
*Chirality* **2004**, *16*, 126-130.

8. Moltzen, E.K.; Bang-Andersen, B.
Serotonin reuptake inhibitors: The corner stone in treatment of depression for half a century – a medicinal chemistry survey. (*Review*).
*Current Topics in Medicinal Chemistry* **2006**, *6*, 1801-1823.

9. Madsen, C.; Jensen, A.A.; Liljefors, T.; Kristiansen, U.; Nielsen, B.; Hansen, C.P.; Larsen, M.; Ebert, B.; Bang-Andersen, B.; Krogsgaard-Larsen, P.; Frølund, B.
5-Substituted imidazole-4-acetic acid analogues: Synthesis, modeling, and pharmacological characterization of a series of novel γ-aminobutyric acid$_C$ receptor agonists.
*J. Med. Chem.* **2007**, *50*, 4147-4161.

10. Hertel, P.; Didriksen, M.; Pouzet, B.; Bretnum, L.T.; Søby, K.K.; Larsen, A.K.; Christoffersen, C.T.; Ramirez, T.; Marcus, M.M.; Svensson, T.H.; Di Matteo, V.; Esposito, E.; Bang-Andersen, B.; Arnt, J.
Lu 35-138 ((+)-(*S*)-3-{1-[2-(1-acetyl-2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl}-6-chloro-1*H*-indole), a dopamine $D_4$ receptor antagonist and serotonin reuptake inhibitor: Characterisation of its *in vitro* profile and pre-clinical antipsychotic potential.
*Eur. J. Pharmacology* **2007** *573*, 148-160.

11. Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M.
Palladium-catalyzed aryl amination-Heck cyclization cascade: A one-flask approach to 3-substituted indoles.
*Angew. Chem. Int. Ed* **2008**, *47*, 888-890.

12. Dahl, T.; Tornøe, C.W.; Bang-Andersen, B.; Nielsen, P.; Jørgensen, M.
Palladium-catalyzed three-component approach to Promazine with formation of one Carbon-Sulfur and two Carbon-Nitrogen bonds.
*Angew. Chem. Int. Ed.* **2008**, *47*, 1726-1728.

13. Larsen, S.B.; Bang-Andersen, B.; Johansen, T.N.; Jørgensen, M.
Palladium-catalyzed monoamination of dihalogenated benzenes.
*Tetrahedron* **2008**, *64*, 2938-2950.

14. Eildal, J.N.N.; Andersen, J.; Kristensen, A.S.; Jørgensen, A.M.; Bang-Andersen, B.; Jørgensen, M.; Strømgaard, K.
From the selective serotonin transporter inhibitor Citalopram to the selective norepinephrine transporter inhibitor Talopram: Synthesis and structure-activity relationship studies.
*J. Med. Chem.* **2008**, *51*, 3045-3048.

15. Arnt, J.; Bang-Andersen, B.; Dias, R.; Bøgesø, K.P.
Strategies for pharmacotherapy of schizophrenia. (*Review*).
*Drugs of the future* **2008**, *33*, 777-791.

16. Finnema, S.J.; Halldin, C.; Bang-Andersen, B.; Gulyás, B.; Bundgaard, C.; Wikström, H.V.; Farde, L.
Dopamine $D_{2/3}$ receptor occupancy of Apomorphine in the nonhuman primate brain – A comparative PET study with [$^{11}$C]Raclopride and [$^{11}$C]MNPA.
*Synapse* **2009**, *63*, 378-389.

17. Andersen, J.; Kristensen, A.S.; Bang-Andersen, B.; Strømgaard, K.
Recent advances in the understanding of the interaction of antidepressant drugs with serotonin and norepinephrine transporters. (*Review*).
*Chem. Commun.* **2009**, 3677-3692.

18. Idris, N.; Neill, J.; Grayson, B.; Bang-Andersen, B.; Witten, L.M.; Brennum, L.T.; Arnt, J.
Sertindole improves sub-chronic PCP-induced reversal learning and episodic memory deficits in rodents: Involvement of 5-$HT_6$ and 5-$HT_{2A}$ receptor mechanisms.
*Psychopharmacology* **2010**, *208*, 23-36.

19. Andersen, J.; Olsen, L.; Hansen, K.B.; Taboureau, O.; Jørgensen, F.S.; Jørgensen, A.M.; Bang-Andersen, B.; Egebjerg, J.; Strømgaard, K.; Kristensen, A.S.
Mutational mapping and modeling of the binding site for (*S*)-Citalopram in the human serotonin transporter.
*J. Biol. Chem.* **2010**, *285*, 2051-2063.

20. Finnema, S.; Bang-Andersen, B.; Wikstrom, H. Halldin, C.
Present State of Agonist Radioligands for Imaging of Brain Dopamine D2/D3 Receptors In Vivo with Positron Emission Tomography.
*Submitted to Current Topics in Medicinal Chemistry.*

21. Arnt, J.; Bang-Andersen, B.; Grayson, B.; Bymaster, F.; Cohen, M.; DeLapp, N.; Glethlen, B.; Kreilgaard, M.; McKinzie, D.; Neill, J.; Nelson, D.; Nielsen, S.M.; Poulsen, M.; Schaus, J.; Witten, L.
Lu AE58054, a 5-$HT_6$ antagonist with pro-cognitive potential.
*Submitted to The Int.J. of Neuropsychopharmacology.*

BOOK CHAPTERS

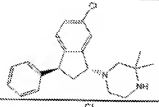
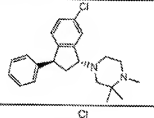
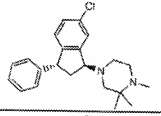
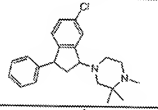
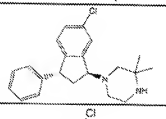
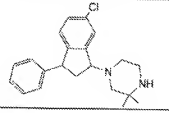
1. Bøgesø, K. P.; Bang-Andersen, B.
Dopamine and serotonin receptor and transporter ligands.
*In* Textbook of drug design and discovery; 3rd ed.; Krogsgaard-Larsen, P.; Liljefors, T.; Madsen, U., Eds.; Taylor & Francis: London, **2002**; pp 299-327.

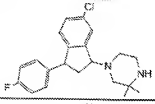
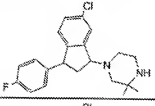
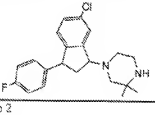
2. Bang-Andersen, B.; Bøgesø, K. P.
Dopamine and serotonin.
*In* Textbook of drug design and discovery; 4th ed.; Krogsgaard-Larsen, P.; Strømgaard, K.; Madsen, U., Eds.; CRC Press, Taylor & Francis Group LLC, Boca Raton, FL, USA, **2010**; pp 299-312.

PATENTS AND CONFERENCE ABSTRACTS/PROCEEDINGS

35 patent applications and >50 conference abstracts/proceedings

## Appendix B

| Compound ID | Compound Structure | Compound Name | CYP2D6 $IC_{50}$ (μM) | Control CMP CYP2D6 (Fluvoxamine) $IC_{50}$ (μM) | Test Date |
|---|---|---|---|---|---|
| Compound I |  | *trans*-1-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine<br><br>(enantiomer of Cpd E) | 7.9*<br><br>5.4** | 10.8*<br><br>8.1** | 30-Aug-02*<br><br>20-Feb-03** |
| Compound A |  | *trans*-4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine<br><br>(enantiomer of Cpd C) | 0.1 | 2.8 | 20-Jul-01 |
| Compound B |  | *trans* -4-((*1S,3R*)-6-chloro-3-phenyl-2,3-dihydro-1H-inden-1-yl)-1,2,2-trimethylpiperazine<br><br>(enantiomer of Cpd C) | <0.02 | 7.8 | 20-Dec-06 |
| Compound C |  | (±)-*trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine<br><br>(racemate of Cpds A & B) | 0.93 | 8.1 | 24-Aug-01 |
| Compound D |  | *trans*-1-((*1S,3R*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine<br><br>(enantiomer of Cpd E) | 0.2 | 2.6 | 3-Jun-03 |
| Compound E |  | (±)-*trans*-1-(6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine<br><br>(racemate of Cpds I & D) | <0.05 | 2.1 | 24-Jul-01 |

| Compound ID | Compound Structure | Compound Name | CYP2D6 $IC_{50}$ (μM) | Control CMP CYP2D6 (Fluvoxamine) $IC_{50}$ (μM) | Test Date |
|---|---|---|---|---|---|
| Compound F |  | *trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine<br><br>(enantiomer of Cpd H) | 1.3 | 10.9 | 3-Feb-03 |
| Compound G |  | *trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine<br><br>(enantiomer of Cpd H) | 9 | 6.9 | 7-Aug-02 |
| Compound H |  | (±)-*trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine<br><br>(racemate of Cpds F & G) | 2.7 | 6.9 | 25-Oct-04 |

*batch 1; **batch 2